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11

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/111,911	07/08/98	WOLD	W 16153-5587
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HM22/0714

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LEE, G

ART UNIT

PAPER NUMBER

1632

DATE MAILED:

07/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/111,911

Applicant(s)
William S. M. Wold

Examiner
Gai (Jennifer) MI Lee

Group Art Unit
1632

- ☐ Responsive to communication(s) filed on _____
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

- ☒ Claim(s) 1-25 is/are pending in the application.
- Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-25 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claims _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____.
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice of References Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

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Response to Arguments

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicants amendment and declaration of Dr. William S. Wold under 37 C.F.R. § 1.132 filed April 12, 2000 in Paper No. 5-6 are acknowledged. Claims 1, 10, 17, 23 and 24 have been amended in applicants amendment filed April 12, 2000. **Claims 1-25 are pending in this application.**

Claim Rejections - 35 USC § 112

Rejection of claims 1-3,5-12,14-19,21-24 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is moot in view of the new grounds of rejection below.

Claims 1, 8-10, 14-17 and 21-23 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition and a method for inhibiting/decreasing apoptosis comprising direct administration of an effective amount of a Receptor Internalization and Degradation (RID) complex having a RID α and RID β polypeptide to the target cells in a liposome which facilitates entry into a cell, does not reasonably provide enablement for any and all routes of administration of a RID polypeptide complex for the treatment of any and all diseases/disorders treated by inhibiting or decreasing apoptosis in any and all patient. The

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specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 8-10, 14-17 and 21-23 are directed to a method for inhibiting or decreasing apoptosis of a cell comprises administering an effective amount of a RID complex to treat the cell and wherein the RID complex is administered with a carrier which facilitates delivery of the RID complex into the cells (claims 1, 8 and 9). In further embodiment, a method for decreasing apoptosis of target cells in a patient comprising treating the patient with an effective amount of RID complex wherein the patient is suffers from a degenerative disease or an immunodeficiency disease and administered with carrier which facilitates delivery of the RID complex into the cells (claims 10 and 14-16). In further embodiment, a method for decreasing leukocyte apoptosis in a patient comprising: (1) withdrawing leukocytes from the patient, (2) treating the leukocytes with an effective amount of a RID complex having a RID α polypeptide and a RID β polypeptide, and (3) administering the treated leukocytes to the patient. (claims 17 and 21) wherein the RID complex is administered with a carrier which facilitates delivery of the RID complex into the leukocytes (claim 22). In further embodiment, a composition comprising a Receptor Internalization and Degradation (RID) complex and a pharmaceutically acceptable excipient, where the RID complex includes a RID α polypeptide and a RID β polypeptide (claim 23).

The specification discloses that RID complex can be isolated from the membranes of Ad-infected cells or cells transfected with a nucleotide sequence encoding the RID α and RID β

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polypeptides or the complex can be expressed in separate cell cultures, extracted into an appropriate buffer and mixed in vitro or RID polypeptides can also be chemically synthesized and mixed to form the complex and use to test for the ability to inhibit apoptosis of a cell expressing a death receptor for Fas and TNFR1 (page 14). The specification further discloses that the RID complex is administered with a carrier that facilitates delivery of the RID complex into the cell, such as liposomes wherein the liposomes can have targeting moieties exposed on the surface such as antibodies, ligands or receptors to specific cell surface molecules to limit delivery of RID to targeted cells (page 14) or one or more of the polypeptides of the complex can be modified to include a specific transit peptide that is capable of delivering the peptide into the cytoplasm of a cell or the complex can be delivered directly into a cell by microinjection (page 15).

The specification discloses that the claimed method is for inhibiting apoptosis or decreasing apoptosis of a cell of a subject comprising treating the cell with an effective amount of a RID polypeptide complex wherein the subject is suffering from a degenerative disease or an immunodeficiency disease. However, the claims are not enabled as the specification does not provide a correlation between RID delivery to the alleviating degenerative disease or an immunodeficiency disease. In particular, a treatment protocol is not described for RID polypeptide complex. The specification addressed the issue of dosage by stating that the specific dose is calculated according to the approximate body weight or body surface area of the patient or the volume of body space to be occupied and that the dose will also be calculated dependent

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upon the particular route of administration selected (page 16). The specification failed to address the level of normalized amount specific to the damage equal the dosage for therapy without administering an overt amount of RID polypeptide complex that could inhibit other tissues in need of apoptosis. The specification states that the compositions and methods of the invention are contemplated for use in promoting survival of tissue transplant wherein the tissue can be treated *in vitro* with the RID complex and the treated tissue then introduced into the transplant (page 16). Thus, this lacks in treatment protocol for polypeptide therapy and the correlation to treating a patient suffering from a degenerative disease or an immunodeficiency disease. The specification does not provide any readily available examples under the meaning of *In re Wands* that effectively demonstrate RID polypeptide interaction or its determining factor toward the inhibition of apoptosis of a therapeutic treatment for degenerative disease or an immunodeficiency disease in which the specification only permits the determination of an *in vitro* method of administering to the cell a plasmid/adenovirus encoding a RID polypeptide complex in inhibiting Fas-mediated apoptosis. The specification fails to correlate the polynucleotide delivery to determining the efficiency of RID polypeptide complex in inhibiting apoptosis. The specification also fails to disclose any and all routes of delivery of the RID polypeptide complex. Without such guidance, the artisan at the time of filing would not be able to implement the claimed invention without an undue amount of experimentation and without a reasonable expectation of success.

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The breadth of the claims is drawn to any and all disease/disorder and any and all routes of administration in any and all patient as broadly claimed, the specification fails to demonstrate RID polypeptide as correlative to treating degenerative disease or immunodeficiency disease. The courts have stated that reasonable correlation must exist between scope of a right to exclude a patent application and scope of enablement set forth in patent application. 27USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving treatment of any and all disease/disorder and any and all routes of administration as broadly claimed, the lack of direction or guidance provided by the specification was well as the absence of working examples with regard to a therapeutic effect treating degenerative disease or immunodeficiency disease by protein therapy, it would have required undue experimentation of one skilled in the art to use the claimed invention as broadly claimed.

Claims 1-7, 10-14, 17-20 and 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition and a method of inhibiting apoptosis or decreasing apoptosis comprising direct administration of an adenovirus vector wherein the adenovirus vector is 231-10 vector containing a polynucleotide encoding the RID complex and wherein the RID complex is expressed in a cell wherein the cell is a leukocyte and expresses Fas, TNFR-1, DR3, TRAIL-R1 or TRAIL-R2, does not reasonably provide enablement for any and all route of administration and treating any and all patients suffering from any and all

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diseases/disorders such as degenerative disease or immunodeficiency disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting/decreasing apoptosis of a cell comprises administering a polynucleotide encoding RID complex or a recombinant adenovirus vector containing a polynucleotide encoding the Receptor Internalization and Degradation (RID) complex in a subject (claims 1-3 and 10-12) wherein the recombinant adenovirus vector is 231-10 (claims 4, 13 and 20). In particular, the method wherein the cell expresses RID and wherein the cell expresses Fas, TNFR-1, DR3, TRAIL-R1, or TRAIL-R2 in a transplant tissue or a patient suffering from a degenerative disease or an immunodeficiency disease of both *in vitro*, *ex vivo* and *in vivo* methodology (claims 5-7 and 17). In particular, the method wherein the patient suffers from a degenerative disease or an immunodeficiency disease (claim 14). In further embodiment, a method for decreasing leukocyte apoptosis in a patient comprising: (1) withdrawing leukocytes from the patient, (2) treating the leukocytes with an effective amount of a polynucleotide encoding RID complex having a RID α polypeptide and a RID β polypeptide, and (3) administering the treated leukocytes to the patient. (claims 17-19). In further embodiment, a recombinant adenovirus comprising a polynucleotide encoding a RID complex operably linked to a promoter, wherein the adenovirus is replication defective and wherein the polynucleotide is expressed upon infection of a eukaryotic cell with the adenovirus and wherein the adenovirus consisting of 231-10 (claims 24-25).

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The specification discloses a *rec700* mutant adenovirus E1B and E3 proteins and 231-10 vector for the delivery of a polynucleotide encoding the RID complex to several cell lines as examples which illustrate the RID complex efficiency to inhibit/down-regulate apoptosis by Fas-mediated apoptosis pathways and TNFR1 (Example 17-35). The specification further discloses the removal or degradation of Fas and TNFR1 from the cell surface by *rec700* (pages 24-30). The specification also demonstrated RID inhibits killing of Ad-infected cells by natural killer cells and cytotoxic lymphocytes. Example 9, discloses 231-10 vector prevents rejection of human cancer cell transplantation into immunocompetent mice. Cancerous cells A549 grew as a tumor in immunocompetent mice which would have been rejected when transplanted in C57BL/6 mice and thus, the RID **should** inhibit rejection by removing Fas and TNFR1 from the transplanted cells (page 30-31). As such, the claim is enabled for inhibiting apoptosis *in vitro*, in so far as the claim is specifically directed to contacting a cell line with an expression vector comprising a nucleic acid encoding RID complex in operable linkage with a promoter. The specification supports this as Example 1-9 demonstrate the *in vitro* use of an expression vector encoding RID complex for the inhibition of apoptosis of a cell.

As for targeting, Applicant's specification fails to provide guidance to the skilled artisan on the parameters for gene delivery (targeting) for the breadth of the claimed invention. Eck & Wilson (The Pharmacological Basis of Therapeutics, 1996) teach numerous factors complicate the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of

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clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. reviews the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain is a 1998 publication which indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (published in 1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each

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and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the “search for such [useful] combinations is a case of trial and error for a given cell type” (page 240, sentence bridging columns 2 and 3). Crystal also reviews various vectors known in the art and indicates that “among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated” (page 409). The specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by any other mode of delivery. The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation. Instead, the specification only teaches a recombinant adenoviral vector construct containing a nucleic acid encoding RID polypeptide complex as an indicator or potential use to down-regulate apoptosis by death receptors as a method of treating any and all disease/disorders such as degenerative disease or immunodeficiency disease.

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The specification, example 9, page 30-32 only states that tumor growth is observed since inhibition of apoptosis has occurred when human A549 cancer cells were not rejected when administered into immunocompetent mouse but there is also no indication of controls in response to mock or non-infected tumor cells with or without the administration of an adenovirus vector encoding RID complex. Furthermore, how does the example of growth of tumors in an immunocompetent mouse correlate to graft retention on the basis of modulation of apoptosis or the correlation between decreased apoptosis in tumor cells relate to decrease apoptosis in leukocytes to an effect on transplant tissue? As such, evidence pertaining to a specific vector, gene, promoter, route of administration, and therapeutic effect must be correlative to what is claimed, and in the instant application, a correlation or nexus cannot be drawn for the reasons discussed above. Without such guidance, the artisan at the time of filing would not be able to implement the claimed invention without undue amount of experiment and without a reasonable expectation of success.

Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect. As the claims are not limited to any specific embodiment of gene therapy nor shown direct correlative effect to treating a patient suffering from a degenerative disease or immunodeficiency

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disease, despite the *in vitro* demonstration of infection of the adenovirus encoding RID complex was sufficient to protect tumor cells from being rejected in C57BL/6 and Balb/c mice from the Examples in the specification.

Accordingly, the breadth of the claims directed to any and all diseases/disorders and any and all routes of administration in any and all subjects as broadly claimed, the specification fails to demonstrate a polynucleotide encoding RID complex as correlative to treating degenerative disease or immunodeficiency disease. The courts have stated that reasonable correlation must exist between scope of a right to exclude a patent application and scope of enablement set forth in patent application. 27USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving treatment of any and all disease/disorder and any and all routes of administration as broadly claimed, the lack of direction or guidance provided by the specification was well as the absence of sufficient working examples with regard to a therapeutic effect treating degenerative disease or immunodeficiency disease, it would have required undue experimentation of one skilled in the art to use the claimed invention as broadly claimed.

Applicant's arguments and declaration filed April 12, 2000 have been fully considered and are found to be persuasive because to defining the previous rejection under 35 USC § 112, first paragraph as containing subject matter which was not described in the specification in such a

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way as to enable one skilled in the art such as effective amounts, effective frequencies, and stability of delivery of the complex or gene, or vectors containing the RID complex sequence and promoters regulating the expression of the RID sequence to obtain a meaningful supply of expressed RID complex to the target cell. However, the claims that are addressed encompass any and all routes of administration for any and all diseases/disorders for treating any and all patients which are subjected to maintaining the enablement rejection under 35 USC § 112, first paragraph directed to the breadth of the claims as stated in the instant application.

Rejection of claims 4, 13, 20, and 25 under 35 U.S.C. 112, first paragraph as failing to provide an enabling disclosure and does not meet with public availability is maintained for the reasons of record and detailed below.

Applicant argues that deposit of adenoviral vector 231-10 is not necessary to practice the invention, as this vector is disclosed in the specification as to provide a repeatable method of the production of the 231-10 plasmid. Applicant's arguments have been carefully considered, but are not deemed persuasive because public availability is not guarantee.

Every patent must contain a written description of the invention sufficient to enable a person skilled in the art to which the invention pertains to make and use the invention. Where the invention involves a biological material and words alone cannot sufficiently describe how to make and use the invention in a reproducible manner, access to the biological material may be necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. Courts have recognized the necessity and desirability of permitting an applicant for a patent to supplement the written disclosure in an application with a deposit of biological material which is essential to meet some requirement of the statute with respect to the claimed invention. *Merck*

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and Co., Inc. v. Chase Chemical Co., 273 F. Supp. 68, 155 USPQ 139 (D. N.J. 1967); *In re Argoudelis*, 434 F.2d 666, 168 USPQ 99 (CCPS 1970). To facilitate the recognition of deposited biological material in patent applications throughout the world, the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure was established in 1977, and became operational in 1981. The Treaty requires signatory countries, like the United States, to recognize a deposit with any depository which has been approved by the World Intellectual Property Organization (WIPO). See MPEP 2402.

Rejection of claims 1-25 contains the term "RID" is vague and indefinite such that the metes and bounds of the claims can not be readily established is withdrawn in view of applicants amendment to the claims filed April 12, 2000.

Rejection of claim 23 has being vague and indefinite in its recitation of "suitable" is moot in view of applicants amendment of the claim filed April 12, 2000.

Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 10 and 17 are incomplete and render the claims vague and indefinite. It is unclear how the step of the method, "an effective amount of a Receptor Internalization and Degradation complex" correlates to the intended effect of the method (the preamble) "inhibiting apoptosis or decreasing apoptosis or decreasing leukocyte apoptosis" since, in light of the specification, mere RID complex alone would not be sufficient to achieve such inhibition without

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the expression of an effective amount of a polynucleotide encoding the RID complex such that cell apoptosis is inhibited within said cell. Amendment to the claim is requested. **Note**, claims 2-9 depend from claim 1, claims 11-16 depend from claim 10, and claims 18-22 depends from claim 17.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claims are drawn to methods of inhibiting/decreasing apoptosis of a cell comprises administering an effective amount of a RID complex or a recombinant adenovirus vector containing a polynucleotide encoding the Receptor Internalization and Degradation (RID) complex in a subject (claims 1-3 and 10-12). In particular, the method wherein the cell expresses RID and wherein the cell expresses Fas, TNFR-1, DR3, TRAIL-R1, or TRAIL-R2 (claim 5). In further embodiment, a recombinant adenovirus comprising a polynucleotide encoding a RID complex operably linked to a promoter, wherein the adenovirus is replication defective and wherein the polynucleotide is expressed upon infection of a eukaryotic cell with the adenovirus.

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Claims 1-3, 5, 10-13 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Dimitrov et al (Apr. 1997), J. of Virology, Vol. 71 (4): 2830-2837.

Dimitrov et al teach an adenovirus E3-10.4K/14.5K protein complex independently inhibits tumor necrosis factor (TNF)-induced apoptosis in Ad-infected cells (abstract). Dimitrov et al also teach several E3 Ad mutant phenotypes such as *pm760* which overexpresses both E3-10.4K and E3-14.5K for inhibition of TNF-induced AA release and apoptosis with A549 cells (page 2831, Materials and Methods, See Table 1). Dimitrov et al further teach that TNF-induced translocation of cPLA₂ was blocked in cells infected with *rec700* but not with *dl763*, a mutant that lacks E3-14.5K and E3-14.7K and thus, E3-10.4K and E3-14.5K function in concert to block TNF-induced AA release and apoptosis by preventing translocation of activated cPLA₂ to membranes. Thus, Dimitrov et al clearly anticipated claims 1-3, 5, 10-13 and 24 of the instant invention.

Claims 1-3, 5-6, 8-12, 15-16 and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Krajcsi et al (Aug. 1996), J. of Virology, Vol. 70 (8): 4904-4913.

Krajcsi et al teach an adenovirus E3-10.4K/14.5K complex and the E3-10.4K/14.5K complex of proteins which independently inhibit TNF-induced apoptosis, also independently inhibits TNF-induced release of arachidonic acid. Krajcsi et al further teach that the E3 10,400-kDa and 14,500-kDa proteins, which function as a heterodimer named E3-10.4K.14.5K inhibited TNF cytotoxicity in 11 of 15 mouse cell lines examined but that in human (but not mouse) cells, the Ad E1B-19K protein inhibits TNF cytotoxicity of infected or transfected cells (p. 4904, column 2).

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Several mutants were disclosed to evaluate the function of E3-10.4K/14.5K in inhibiting TNF cytolysis but also to prevent a TNF-induced inflammatory response (page 4905, Materials and Methods, column 2). Krajcsi et al also teach that for E3-10.4K/14.5K, the step inhibited could be at the cell surface, perhaps the TNF receptor or the unknown proteins that couple the receptor to downstream signaling molecules that activate cPLA₂ in U937 cells. Thus, Krajcsi et al clearly anticipated claims 1-3, 5-6, 8-12, 15-16 and 24 of the instant invention.

Claims 1-3, 5, 8-12, 15-16 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al (Jan. 1995), J. of Virology, Vol. 69 (1): 5871-5881.

Stewart et al teach an adenovirus E3 10.4K and 14.5K proteins (two protein function as a complex), which function to prevent/protect cytolysis by tumor necrosis factor and to down-regulate the epidermal growth factor receptor, are localized in the plasma membrane. Stewart et al further teach that both proteins are localized in the plasma membrane and that trafficking of each protein to the plasma membrane depends on concomitant expression of the other protein and that neither protein is secreted (abstract). Stewart et al teach several mutants of the E3 region such as *rec700* and *pm760* to observe the preventive or protective function of the E3 region proteins in human KB cells, A549 and A431 cells (page 173, Material and Methods, column 1). Stewart et al also teach that 10.4K-14.5K complex blocks TNF cytolysis by interfering with the function of one or more of the membrane-associated proteins that participate in TNF signaling (page 180,

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column 2). Thus, Stewart et al clearly anticipated claims 1-3, 5, 8-12, 15-16 and 23-24 of the instant invention.

Conclusion

Claims 4, 7, 13-14, 17-22 and 25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1-3, 5-6, 8-12, 15-16 and 23-24 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasmine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

**Gai (Jennifer) Lee
Patent Examiner
Art Unit 1600**

Gai Mi Lee
Patent Examiner
1632